IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	VAN DEN MOOTER et al.	Confirmation No.:	2958
Serial No.:	10/595,119	Art Unit:	1615
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Customer No.:	21559		
Title:	PARTICLE SIZE REDUCTION OF BIOACTIVE COMPOUNDS		

REQUEST FOR REPUBLICATION PURSUANT TO 37 C.F.R. § 1.221(b)

Applicants request republication of the above-captioned patent application under 37 C.F.R. § 1.221(b). This request for republication is being filed within two months from the date of the patent application publication. Applicants request correction of the following material errors made by the Office:

(1) On page 10, right column, line 15 of the published application, the phrase "0.5 nm to 10 μm" of claim 38 should appear as "0.5 μm to 10 μm," as shown on page 4, line 3 of the Preliminary Amendment filed concurrently with the application on February 23, 2006.

A marked up copy of the relevant page of the publication accompanies this request.

If there are any charges or any credit, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 6/4/2007

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of this suspension in a pre-cooled ball that was kept in liquid nitrogen followed by freeze-drying. Another part of the suspension was pumped through a series of 9 consecutive magnetic devices according to the set-up of FIG. 2C with the same conditions as described herein. At the outlet of said magnetic system, the suspension was immediately solidified in a pre-cooled ball that was kept in liquid nitrogen and followed by lyophilisation. The dissolution profiles of these untreated and magnetically treated samples are given in FIG. 12.

[0082] Dissolution experiments were performed in a SR8 PLUS Hanson dissolution test station (commercially available from Chatsworth, United States) while using the USP 24 method (paddle method, 100 rpm). Samples (corresponding to 16.7 mg of loperamide) were added to 500 ml of dissolution medium being a solution of 0.005 M potassium hydrogen phthalate (commercially available from Acros Organics, Geel, Belgium) and 0.00192 N NaOH in water and the temperature of the dissolution medium was maintained at 37±0.1° C. Samples of 2 ml were taken and immediately replaced with fresh dissolution medium at 10, 20, 30, 45, 60 and 120 minutes respectively and then filtered with PVDF filters of 0.45 μm (commercially available from Acrodisc, Pall Corporation, New York, United States) into HPLC vials (1.5 ml, commercially available from Merck, Darmstadt, Germany). The corresponding concentrations were determined from the calibration curve with HPLC.

[0083] The HPLC system used for this determination consisted of LiChroGraph® L-7100 HPLC pump, an autosampler model L-7200 equipped with a 100 μl loop, a UV detector model L-7400 set at 220 nm, and an Interface D-7000, all from commercially available from Merck-Hitachi (Darmstadt, Germany). UV signals were monitored and peaks were integrated using the D-7000 HSM software. All chromatographic separations were performed at room temperature. The column used was Hypersil BDS C18 (commercially available from Merck, Darmstadt, Germany). The mobile phase consisted of a 0.001 M acetonitrile/tetrabutylammonium hydrogen sulfate mixture (30:70 by volume) and was degassed by ultrasonication before use. The flow rate amounted to 1 ml/minute. The retention time of loperamide at these conditions was 7 minutes.

[0084] Both in the presence of a silicate (Aerosil) and in the presence of a surfactant (Tween 80), FIGS. 11 and 1 show that the dissolution rate of loperamide is significantly increased by the magnetic treatment of the invention in comparison with the corresponding untreated samples.

1-32. (canceled)

33. A method for reducing the average size of biologically active compound solid particles or agglomerates suspended in a liquid by flowing one or more times said liquid having biologically active compound solid particles or agglomerates suspended therein through one or more magnetic fields to reduce the average size of a substantial portion of the biologically active compound solid particles or agglomerates by at least 25%, wherein the linear flow rate of said liquid through each said magnetic field is between 0.25 and 25 m/s.

34. A method according to claim 33, wherein the strength of each said magnetic field is at least about 2,000 gauss.

35. A method according to claim 33, wherein the average size of said biologically active compound solid agglomerates before performing said method is in a range from 10 μm to 100 μm.

36. A method according to claim 33, wherein the average size of a substantial portion of said biologically active compound solid agglomerates after performing said method is reduced to a range from about 0.45 μm to 5 μm.

37. A method according to claim 33, wherein said substantial portion is at least 50% by weight of the suspended solid agglomerates.

38. A method according to claim 33, wherein the average particle size of said biologically active compound solid particles before performing said method is in a range from ~~0.5 nm to 10 μm~~. **0.5 μm to 10 μm.**

39. A method according to claim 33, wherein the average particle size of said biologically active compound solid particles after performing said method is reduced to a range from 0.5 nm to 500 nm.

40. A method according to claim 33, wherein said liquid is water or an organic solvent or a combination thereof with water.

41. A method according to claim 33, wherein said biologically active compound solid particles or agglomerates are suspended in said liquid in the form of a slurry and the concentration of said biologically active compound solid particles or agglomerates in said liquid is at least two times the solubility limit of said biologically active compound in said liquid under the physical (temperature, pressure) and chemical (pH) conditions prevailing while flowing said slurry through said magnetic field.

42. A method according to claim 33, wherein said liquid includes one or more stabilizing agents.

43. A method according to claim 33, wherein the residence time of said liquid through each said magnetic field is between 60 microseconds and 10 seconds.

44. A method according to claim 33, wherein the biologically active compound is in a crystalline form or an amorphous form.

45. A method according to claim 33, wherein the biologically active compound is a drug classifiable as Class II or Class IV of the Biopharmaceutical Classification System.

46. A method according to claim 33, wherein the biologically active compound is a drug having a water-solubility below 2 mg/ml.

47. A method according to claim 33, wherein the biologically active compound is a cosmetic agent, a diagnostic agent, a herbicide, an insecticide, a biocide or a fungicide.

48. A process for manufacturing a biologically active compound formulation, said biologically active compound being in the form of solid particles or agglomerates, said process comprising a step of reducing by at least 25% the average size of a substantial portion of said biologically active compound solid particles or agglomerates by suspended them in a liquid and by flowing one or more times said liquid having biologically active compound solid particles or agglomerates suspended therein through one or more magnetic fields.

49. A process according to claim 48, wherein said process further comprises one or more post-processing steps performed following the size reducing step.

50. A process according to claim 48, wherein said post-processing step is a drying step for substantially removing